

## Abstract

We have developed a novel computational approach to functional de novo protein design using gradient based continuous optimization techniques. Motivated by many engineering applications in which a cost function is optimized subject to a set of constraints, we pose a functional protein design task as a continuous optimization problem to search sequence and conformation spaces simultaneously. The methods used in sequence-space search are analogous to the material-design formulations in the topology optimization of structures, whereas the conformation search techniques are similar to mechanical-link like models and modal analysis of structures. Computationally efficient techniques such as the nonlinear conjugate gradient and interior point optimization are used to solve optimization problems. Both the sequence and conformation search techniques are individually validated with real proteins. Coarse-grained as well as atomistic potentials are used to model the energy. Finally, we combine the sequence and conformation search methods and propose a new strategy for a simultaneous search in sequence and conformation spaces for designing functional de novo proteins. In view of the lack of experimental resources, the proposed computational scheme is validated by re-designing an existing protein, the hen-egg white lysozyme. Since the thrust of this method is on developing computationally efficient models, we developed an amino acid grouping scheme based on metric multi-dimensional scaling. Some structure-prediction problems are also solved using Graphics Processing Unit (GPU) based Compute Unified Device Architecture (CUDA) programming.